# REMARKS

Claims 1-33 are pending.

Claims 1-4, 11, 12, 14, 16, 17, 21, 22, 24-28 and 31 have been amended for clarity and to correct for typographical errors. No new matter has been added.

Reconsideration in light of the following remarks is respectfully requested.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

**Restriction Requirement**

Claims 27, 28 and 33 are withdrawn.

The Examiner has withdrawn claims 2, 4, 12, 14, 17, 19, 22 and 24 as being drawn to a nonelected group or elected modification. Applicants respectfully traverse. On page 2 of the instant Office Action, the Examiner stated that claims reciting elected modifications at positions 223, 225, 226, 237 and 269, as well as combinations of those elected modifications will be considered. Claims 2, 4, 12, 14, 17, 19, 22 and 24 each recite the combination 225/269. Applicants therefore request that the Examiner examine claims 2, 4, 12, 14, 17, 19, 22 and 24.

The Examiner has withdrawn claim 31 as being drawn to a nonelected group or elected modification. Applicants respectfully traverse. The Examiner in the Requirement for Restriction/Election of June 9, 2006, required that Applicants select "5 variant modifications of RANKL proteins from claim 1[.]" These modifications refer to point mutations. Claim 31 recites modifications such as PEGylation, glycosylation and fusion to another entity that do not entail substitution of one amino acid for another. Thus,

Applicants submit that claim 31 reads on the originally elected species and request the Examiner examine claim 31.

**Sequence Listing**

The Examiner has required correction of the specification in order to comply with Sequence Rules and Regulations. Applicants have amended the specification and believe that it complies with the Sequence Rules.

**Claim Rejections - 35 USC 112, first paragraph**

The Examiner has rejected claims 1, 3, 5-11, 13, 15, 16, 18, 20, 21, 23, 25, 26, 29, 30 and 32 under 35 USC 112, first paragraph, for allegedly lacking enablement for a variant protein wherein said variant RANKL protein wherein said variant RANKL comprises modifications at positions R223, H225, E226, Q237, and E269.

Applicants have amended claim 1 to recite a modification at C221 and I247. Applicants have also amended claims 3-5, 13, 19, 23, 24, 26 and 28 to recite substitutions C221S and I247E.

With respect to claim 32, the Examiner states that it could not be predicted that the cell culture data presented in the specification would correlate with therapeutic agents for in vivo treatments.

In rejecting claim 32, the Examiner cited a 1983 treatise by Freshney. Notably, Freshney does not teach, explicitly or implicitly, that binding studies of a compound carried out *in vitro* cannot be correlated to a therapeutic effect *in vivo*. In Freshney's treatise, differences between cell behavior *in vitro* and *in vivo* relate primarily to cell proliferation and metabolism. However, whether a cell propagates in three-dimensional space *in vivo* or in two-dimensional space *in vitro* has no bearing on whether it differentiates into an osteoclast due to RANKL binding. Furthermore, the fact that "[e]nergy metabolism *in vitro* occurs largely by glycolysis" is irrelevant to osteoclast differentiation. Freshney thus does not support the assertion that art is unpredictable

with regard to the difference between RANKL binding effects *in vivo* and *in vitro*. The assertion by Freshney in 1983 that differences between *in vitro* cells and *in vivo* tissue "has often led to tissue culture being regarded in a rather skeptical light" is contradicted by years of science and law wherein recognition of the correlation between *in vitro* cultures and *in vivo* effects is routine. In fact, Freshney himself admits in conclusion that "it must be emphasized that many specialized functions are expressed in culture and as long as the limits of the model are appreciated, it can become a very valuable tool."

In the 19 years between publication of the Freshney treatise and this application's 2002 effective filing date, both the law and the art have come to recognize that *in vitro* assays are a valuable tool for identifying compounds that exhibit a pharmacological and therapeutic effect.

"As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a **reasonable** correlation between the activity in question and the asserted utility." MPEP 2107.03(I) (original emphasis; citing *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985)). "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays . . . **almost invariably** will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." MPEP 2107.03(III) (emphasis added).

The Federal Circuit has accepted *in vitro* tests as indicative of the therapeutic utility of a compound. In *Cross v. Iizuka*, 753 F.2d 1040, 1042 (Fed. Cir. 1985), Iizuka, a party to an interference proceeding, disclosed in his patent application imidazole derivatives that inhibit the synthesis of thromboxane synthetase. The Board of Patent Interferences found "pharmacological activity" based on Iizuka's disclosed *in vitro* utility. *Id.* at 1043. The Federal Circuit upheld the holding of the Board of Patent Interferences, stating that "*in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable

correlation therebetween." *Id.* at 1050. The Federal Circuit further noted that "a rigorous correlation [between *in vitro* utility and an *in vivo* activity] is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *Id.*

The Examiner contends that undue experimentation would be necessary for a skilled artisan to practice the claimed invention. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. MPEP 2164.03 (citing *In re Fisher*, 427 F.2d 833 (CCPA 1970). The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. *Id.* What is known in the art provides evidence as to the question of predictability. *Id.*

The use of RAW 264.7 cells in a TRAP assay to identify compounds that therapeutically block osteoclastogenesis is well-known in the art. The specification of the present application (for example at paragraphs 239 and 6) has already clearly incorporated references from the art that set out the correlation between RAW 264.7 assays and the determination of osteoclastogenesis inhibition. More recent studies acknowledge the same correlation. For example, Wang et al., *J Bone Miner Res*, 18, 2159-68 (2003), used RANKL-induced RAW 264.7 cells to assess the effect of a compound on osteoclastogenesis. They note selective modulation of RANKL signaling pathways may have important therapeutic implications for the treatment of bone diseases associated with enhanced bone resorption. *Id., abstract.*

McClung et al. recently published Phase 2 data demonstrating that injections of denosumab, a RANKL inhibitor, significantly increased bone mineral density in a group of postmenopausal women. *N Engl J Med*, 354, 821-831 (2006). Denosumab is a fully human monoclonal antibody that is known to bind RANKL with high affinity, blocking the interaction of RANKL with RANK. *Id.* at 822. The discovery of the RANKL-RANK

pathway as the primary mediator of osteoclast differentiation, activation and survival facilitated the design of molecules that specifically target this pathway for the treatment of osteoporosis. *Id.* at 830 (citations omitted). Thus, McClung et al. show that molecules that are known even before clinical trials and hence *in vitro* to have an effect on the RANKL-RANK pathway are the basis for designing molecules that can be used to treat osteoporosis. Indeed, McClung's antibody, which inhibits RANKL binding to RANK, showed a direct effect on bone mineral density in clinical trials.

The Federal Circuit requires only a reasonable correlation between an *in vitro* assay and *in vivo* activity to demonstrate therapeutic utility. Wang, McClung and references cited in the instant specification indicate that *in vitro* assays of proteins affecting RANKL binding reasonably correlate such proteins with a pharmacological and therapeutic effect. In light of the references cited above, a skilled artisan would reasonably extrapolate the results known in the art to the presently claimed invention. Thus, no undue experimentation would be needed to practice the invention of claim 32.

In light of the above arguments, Applicants request that the Examiner withdraw the rejection.

**Claim Rejections - 35 USC 112, second paragraph**

The Examiner has rejected claims 1, 3, 5-11, 13, 15, 16, 18, 20, 21, 23, 25, 26, 29, 30 and 32 under 35 USC 112, second paragraph, for allegedly being indefinite in the recitation of amino acid positions in the absence of a referenced SEQ ID NO. Applicants have amended claim 1 to recite SEQ ID NO: 1, which refers to amino acids 68-317 (SEQ ID NO: 1) of full-length wild-type human RANKL. In light of the amendment, Applicants request that the Examiner withdraw the rejection.

**Claim Objections**

Applicants have corrected the typographical error in claim 3 and request that the objection be withdrawn.

**Examination of Non-elected Species**

Applicants believe that the claims, at least to the extent that they read on the elected species, are patentable. Applicants therefore request that according to MPEP 803.02 the Examiner withdraw the requirement for election and extend prosecution to the claims as they read on unelected species.

# CONCLUSION

Applicants believe the claims are in a condition for allowance. Early notification thereof is respectfully requested. The Examiner is invited to call the undersigned at 415.442.1000 to resolve any questions. Although Applicants do not believe any additional fees are required, the Commissioner is authorized to charge any additional fees that may be required or to credit any overpayment to Deposit Account No. 50-0310 (Docket No. 067461-5105-US01).

Respectfully submitted,

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